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EDITORIAL

FGF-2: Specific activity in kidney?

Floege et al [1] have set out to determine the specific role of fibroblast growth factor-2 (FGF-2) in the adult kidney. This is a difficult task because the FGF family currently has 19 members (in humans), some of which share up to 70% of their amino acid sequence, and in many assays have similar activities. Thus, unique identifiers are required to define the function of a member of a large family of growth factors. Several approaches to finding these identifiers include: describing an activity that is not replicated by other family members when applied in a physiologically relevant manner; identifying a unique site of expression; and locating a dedicated receptor or unique combination of receptors. Deletion of factors distinguished in these ways should also produce a detectable change in some process. If the specific characteristics of factors are not yet apparent, as in a comparison of two factors with apparently identical expression patterns and activities, the function of the two factors might be suggested by compound deletions.

Specificity of function in the FGF family is now apparent from these types of studies. The expression patterns of FGFs and their receptors are exquisitely specific, suggesting that particular sets of autocrine and paracrine signals are operative. In a striking example (in hair follicles), at least four FGFs and all four FGF receptors are expressed in contiguous domains, some as little as one or two cell diameters thick [2]. Additional specificity for FGF signaling is provided by the differential affinity of FGF receptors for different family members. This results from an alternatively spliced third extracellular immunoglobulin loop (type IIIb or IIIc receptors) and possibly also as a result of variations between the first and second immunoglobulin loops. Binding specificity is also profoundly regulated *in vivo* by additional molecules, specific heparan sulfate proteoglycans, which act as co-receptors for the FGFs. In the absence of any other change in FGF receptor subtypes, changes in heparan sulfates can select between two FGFs and determine which one signals [3]. This additional determinant of ligand-receptor interaction creates greater specificity than may be evident in binding assays performed *in vitro*, which have shown various mixtures of FGF and FGF receptor interactions. *In vivo*, FGF signaling may also be delimited by the presence of inhibitors. These include soluble receptors, which result from alternative exon splicing (for example, type IIIa receptors) or from proteolysis, and the inhibitor of FGF signalling, *sprouty* [4]. Anti-sense RNA might further modulate ligand availability at different times [5].

Mechanisms creating specificity for FGF signaling in the kidney are not established, but there are a number of suggestions. Different FGFs have been found to target different components during development: FGF-2 and -7 are localized to domains contiguous with FGF receptors that have relative specificity for these molecules. Moreover, different proteoglycans are found at different sites in the renal interstitium, suggesting regional control of FGF signaling [6]. Lastly, a soluble dominant negative receptor that binds a number of FGFs can abolish renal development [7]. Since the phenotype of this "compound knockout" is more severe than known single knockouts, the inhibitor blocks either a unique, unidentified FGF, or it abolishes signaling by FGFs that are simultaneously or sequentially required in a specific combination. This type of specificity, derived from combinatory activities of similar factors, has been found in other families of signaling proteins. For example, IL-6 cytokines have identical activities due to shared receptor components. Nevertheless, compound deletions suggest that the growth-promoting or inductive activities of individual cytokines are additive [8].

Less is known about the behavior of FGFs in the adult kidney. To establish the specific activity of one family member, Floege et al [1] have examined the expression pattern of FGF-2 and one of its receptors, flg. Antibodies against both extracellular and intracellular epitopes of flg were used, permitting detection of full-length receptors rather than fragments. The data show overlapping or neighboring expression of ligand and receptor, suggesting autocrine and paracrine signaling in distal tubular segments and paracrine signaling in glomeruli and across the arterial wall. Of course, it will be necessary to map other FGFs and their receptors in order to establish the uniqueness of these FGF-2/flg associations. Also, given that FGF-2 is secreted by a nonclassical pathway [9], and nuclear localization has been found, it will also be necessary to establish when FGF-2 is actually secreted from these sites. The absence of inhibitors of signaling at those locations may also be a prerequisite.

However, there are tantalizing data from FGF-2 knock-

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out animals that may confirm the importance of one of the FGF-2/flg associations found in the current study. The deletion of FGF-2 results in hypotension. The defect appears related both to reduced vascular smooth muscle contractility, as measured in isolated vessels, and to autonomic dysfunction [10, 11]. Perhaps signaling between endothelia and muscle by FGF-2/flg regulates the contractile machinery or its response to other exogenous inputs. Analysis of the renal arterial circulation is now required. The FGF-2/flg association in the distal nephron is also intriguing because the infusion of FGF-2 in normal animals results in Na^+ retention [12]. While such infusions may activate a number of FGF receptors, the finding suggests that one function of the FGF-2/flg association in the distal nephron may be to regulate the final filtrate by modulating ion transport. The localization of FGF-2 in parietal podocytes and flg in the glomerular tuft is striking because it suggests a previously unexpected transglomerular signaling pathway. Perhaps this pathway regulates glomerular hemodynamics. Nevertheless, since FGF-2 augments diseases of the visceral podocyte [13], the current work redirects attention to the parietal cell and its role in initiating and maintaining glomerular disease.

In summary, the findings of Floege [1] produce three separate hypotheses, including the notion that this 'growth factor' regulates cellular functions other than growth. Further anatomical data and physiologic assays in deleted animals will clarify the specific activity of FGF-2 in the adult kidney.

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